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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,073	SEGAL ET AL.	
	Examiner	Art Unit	
	Benjamin P. Blumel	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-82* is/are pending in the application.

4a) Of the above claim(s) *5-9,13,14 and 40-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10-12,15-39 and 79-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/28/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

]DETAILED ACTION

Applicants are informed that further examination of the instant application will be conducted by Examiner Blumel. Contact information is provided below.

Election/Restrictions

Applicant's election of a viral antigen and a ligand for GM-CSF receptor in the reply filed on December 21, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 5-9, 13, 14, and 40-78 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 21, 2006.

Claims 1-4, 10-12, 15-39 and 79-82 are examined in this Office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on October 28, 2003 was filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4 and 34-39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5 and 6 of copending Application No. 10/262,828 in view of Faulkner et al. *see below*. The claimed invention of the co-pending application in view of the teachings of Faulkner et al. with regard to GM-CSF and the correlating receptor being expressed by dendritic cells would be obvious to one skilled in the art to generate the claimed invention.

This is a provisional obviousness-type double patenting rejection.

Claims 1, 2, 4 and 34-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 7 of U.S. Patent No. 6,224,870 B1 in view of Faulkner et al. *see below*.

The patented invention of '870 is drawn to a method of modulating an immune response in a mammal to an antigen by administering an expression cassette that expresses an antigen fused to a secretory signal and a cell surface receptor ligand of a APC. However, the patented

invention does not claim the specific cytokine (i.e. ligand for cell surface receptor) of the instant application. Therefore, in conjunction with the patented invention and in view of the teachings of Faulkner et al. which develop a similar fusion polypeptide comprising an influenza HA molecule fused to IL-2 and also discuss the important consideration of other cytokines such as GM-CSF since dendritic cells possess a cell surface receptor for GM-CSF, *see below*, it would be obvious to one skilled in the art to generate the claimed invention of the instant application.

This is a provisional obviousness-type double patenting rejection.

Claims 1, 2, 10 and 34-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 12, 16, 22 and 23 of U.S. Patent No. 6,403,080 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented invention anticipates that of the claimed invnetion.

Claims 1-4 and 34-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 6,632,436 B2 in view of Faulkner et al.

The patented invention of '436 is drawn to a method of modulating an immune response in a mammal to an antigen by administering an expression cassette that expresses an antigen fused to a secretory signal and a cell surface receptor ligand of a APC. However, the patented invention does not claim the specific cytokine (i.e. ligand for cell surface receptor) of the instant application. Therefore, in conjunction with the patented invention and in view of the teachings of Faulkner et al. which develop a similar fusion polypeptide comprising an influenza HA

molecule fused to IL-2 and also discuss the important consideration of other cytokines such as GM-CSF since dendritic cells possess a cell surface receptor for GM-CSF, *see below*, it would be obvious to one skilled in the art to generate the claimed invention of the instant application.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 10-12, 15-39 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulkner et al. (International Immunology, 2001), Guillett et al. (European Journal of Biochemistry, 2002), Robinson et al. (Proceedings of the National Academy of Science, 1998), Operschall et al. (Journal of Clinical Virology, 1999) and Nobusawa et al. (Virology, 1991).

The claimed invention is drawn to a method of modulating an immune response in an animal with a 10 amino acid fragment of influenza hemagglutinin (HA) fused with a ligand for a cytokine receptor. The animal could be a mammal, such as a human. Additionally, the HA fragment is of the influenza virus A/PR/8/34 and is N-terminal to the ligand. The HA, a naturally occurring Lectin, is capable of binding to a carbohydrate structure with sialic acids. The claimed invention also involves an influenza virus hemagglutinin H2 or H3 or a HA of an influenza that does not infect humans. In addition, the ligand is mouse or human GM-CSF and is fused with the HA antigen via a Gly-Ser linker with the HA antigen at the C-terminus of GM-CSF.

Faulkner et al. teach the development of a chimeric vaccine comprising 10 amino acid region of HA from Influenza virus A/PR/8/34 linked to IL-2 and the importance of researching other chimeric cytokine-antigen vaccines that provide the therapeutic effects of the cytokine with the antigenic properties of the antigen in addition to improving the half-life of the cytokine *in vivo*. Some examples of cytokine candidates are IFN-γ, GM-CSF, IL-4, and IL-10 since the respective receptors are expressed by Dendritic Cells (DCs), which also function as antigen presenting cells, as also discussed by Faulkner et al. Faulkner et al. further teach the use of the HA-IL-2 chimeric in the activation of bone marrow-derived dendritic cells with compared to treatments with separated HA and IL-2. Even though did not administer the chimeric vaccine to an animal, Faulkner et al. observed an increased T cell activation by way of antigen presentation of the chimeric composition from DCs and they also disclose that previous studies pertaining to *in vivo* activity of similar chimeras have been analyzed. However, Faulkner et al. do not teach

the specific fusion of a HA with GM-CSF via a Gly-Ser linker, or with the HA at the C-terminus of GM-CSF, or that the HA is H2, H3 or a HA of an influenza virus that does not infect humans.

Guillett et al. teach linking of a cytokine, cardiotrophin-like cytokine (CLC), with a recombinant neurotrophic factor (CNTF) receptor via a Glycine-Serine linker $(G_4S)_2$. Guillett et al. observed an increase in stability among the chimeric complex.

Robinson et al. teach the identification of an ideal Glycine-Serine linker length and composition for the Arc repressor dimer. Robinson et al. discuss that identifying a linker, which improves desired properties (i.e. flexibility, stability, increased *in vivo* half-life) of a protein complex would prove to be a very important discovery. Through their random Arc-linker-Arc constructs, Robinson et al. identified an ideal linker with 7 serines and 9 glycines.

Operschall et al. teach the co-administration of plasmid DNA that encodes Influenza A/PR/8/34 hemagglutinin and mouse GM-CSF to mice in order to protect against viral infection. Operschall et al. observed that the cytokine-antigen combination possess adjuvant properties.

Nobusawa et al. teach the comparison of 13 HA serotypes of Influenza A viruses. In particular, Nobusawa et al. H2, H3, H8 and H12, of which, H8 and H12 serotype viruses are not known to have infected humans as of yet.

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Faulkner et al. in order to vaccinate with a vaccine comprising an influenza A hemagglutinin protein (H1, H2, H3 or non-human related) linked to GM-CSF via Glycine-Serine linker, thereby inducing an immune response. One would have been motivated to do so, given the suggestion by Faulkner et al. that recombinant influenza HA-cytokine chimeras be used as vaccines to induce cell mediated immunity. There would have been a reasonable expectation of

success, given the knowledge that the stability of a cytokine-heterologous protein chimera improved by a 10-mer linker of Glycine-Serine and in the case of a recombinant repressor which is stabilized by a 16-mer Glycine-Serine linker, as taught by Guillett et al. and Robinson et al., respectively, also given the knowledge that the co-administration of influenza HA and mouse GM-CSF have adjuvant related properties, as taught by Operschall et al., and also given the knowledge that various Influenza A hemagglutinin antigens (H2, H3, H8 and H12) are known based on sequence analysis, as taught by Nobusawa et al. In addition, even though the combined teachings do not address the alternate C-terminus placement of the HA antigen or the use of human GM-CSF, one skilled in the art would modify the claimed fusion protein in order to optimize the cellular-chimera interaction and also to utilize a cytokine that is endogenous to the targeted host, i.e. human GM-CSF. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 10, 15, 17, 81 and 82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes the generation of a vaccine involving influenza

hemagglutinin fused to GM-CSF (Experiments 16, 18 and 19), but the specification does not provide a representative number of species that would indicate that at the time of filing the applicants were in possession of invention of claim 1.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 10-12, 15-26, 34-49 and 79-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. As recited in claim 1, it is unclear what "an antigen bearing target" is. The examiner believes this recitation refers to non-elected species, such as in claim 5, which recites "said antigen bearing target is a cell", but based on the applicants election of a viral antigen it is unclear what the antigen bearing target is referring to. In the case of the viral antigen, i.e. hemagglutinin, the "target" would the virus in which it came from, not the antigen it self. However, as also required in claim 1 and 10-12, the claimed invention requires that the viral antigen be fused to a ligand for a cytokine receptor, but of the target is interpreted to be the virus that donates its antigen, doesn't the virus need to be fused to the ligand to agree with the recitation of claim 1. Please clarify either through explanation of the intended invention or by amending claim 1.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin P. Blumel whose telephone number is 571-272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin P Blumel/
Examiner
Art Unit 1648

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